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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WAX, ROBERT A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/448,946	SINGH, ARJUN	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-54 and 58-64* is/are pending in the application.

4a) Of the above claim(s) *61-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-54 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Office action comes after many years of history of prosecution in this application and is intended to contain all remaining issues. It is contemplated that the remaining issues may be disposed of in the next response from Applicant and prosecution successfully closed thereafter. Any previously made rejections not repeated herein are expressly withdrawn.

Specification

2. The disclosure is objected to because of the following informalities: The newly re-submitted amendment to page 1 does not comply with 37 CFR 1.121. Page, 1, lines 21-23 had been replaced by a preliminary amendment filed with the application on 5/24/95 (see transmittal sheet, item 7). The proposed amendment shows amendment of the text deleted from the specification by the preliminary amendment, not amendment of the text that replaced it. Because this problem has not been adequately addressed by Applicant, Examiner repeats this portion of the Advisory Action mailed June 23, 2004

Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 47-54 and 58-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression vehicle comprising DNA encoding the first 85 amino acids of yeast alpha mating factor pre-sequence ending with arginine operably connected in translation reading frame to DNA encoding human interferon alpha 1 and a process of making functional human interferon alpha 1 with extra amino acids left over on the end, does not reasonably provide enablement for (1) an expression vehicle comprising only the naked promoter sequence or only the pre-pro sequence for yeast alpha factor operably connected to a DNA sequence encoding a protein or method of using it or (2) other yeast alpha mating factor prepro sequences or (3) other functional proteins retaining unprocessed extra amino acids on the end. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 47, 48, 50, 52 and 54 of the instant case correspond to claims 1, 2, 4, 6 and 8, respectively, of grandparent application 06/506,098. In the first action on the merits of that case a rejection was made stating that use of the naked promoter sequence for yeast alpha factor operably connected to a DNA sequence encoding a protein was enabled "only for claims limited in accordance with the disclosure at pages 16 and 17 and Figures 5 and 6 of the specification." That rejection goes on to say, "It appears from applicant's specification and figures that the fragment from p53 which results in p57 contains both the promoter sequences of the α-factor and 89 amino acids (pre-pro) sequence of the α-factor in tandem. However, applicant is claiming either the

promoter or the pre-pro peptide of yeast, not both in tandem as set forth in the specification." This rejection is substantially repeated for the instant claims.

Claims 47, 48, 50, 52 and 54 read on a yeast expression vehicle comprising only the naked promoter sequence or only the pre-pro sequence for yeast alpha factor operably connected to a DNA sequence encoding a protein and methods of making or secreting heterologous proteins with it. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to a yeast expression vehicle comprising only the naked promoter sequence or only the pre-pro sequence for yeast alpha factor operably connected to a DNA sequence encoding a protein and methods of making or secreting heterologous proteins with it.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in

determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, (1) the amount of experimentation is large because the number of possible functional proteins retaining unprocessed extra amino acids on the end is huge which would necessitate a large amount of testing; (2) the amount of guidance provided by the specification is limited because the actual promoter sequence is not disclosed separately and because there is no guidance as to which proteins may retain their function if they are expressed retaining unprocessed extra amino acids on the end. Continuing, (3) the sole working example is expression of functional human interferon alpha 1 retaining unprocessed extra amino acids on the end; (4) the nature of the invention is the discovery of the possibility to use yeast alpha factor control sequences to express and secrete heterologous proteins. The prior art (5) shows that such had not been accomplished before; (6) the relative level of skill in this art is very high; (7) the predictability of the art is low; in fact, this is the predominant Wands factor.

Page 2, lines 10-17 of the specification teaches that, at the time the invention was made, it was known that secreted proteins have evolved with signal sequences that are well suited for secretion of that particular protein through a cell membrane. At page 4, lines 25-27, it is taught that the secretory processes in yeast were not fully understood. It is also stated at page 16, lines 15-17 that the processing steps for yeast

precursor proteins are unpredictably different from those of mammalian precursor proteins.

The specification is also unclear on what constitutes the pre-pro peptide of the mating factor pre-pro polypeptide (page 9, lines 14-17). In view of the examples, it has been assumed that the pre-pro peptide corresponds to an N-terminal peptide of alpha factor with a carboxy terminus ending with Lys-Arg or a Glu-Ala dipeptide. The "protein" recited in the claims that is secreted or recovered may be either mature protein or it may be protein expressed with extra amino acids on the end. As stated, expression of mature proteins is not enabled, nor is expression of functional proteins retaining unprocessed extra amino acids on the end. The specification teaches at page 2, lines 10-17 that at the time the invention was made that secreted proteins have evolved with signal sequences that are well suited for secretion of that particular protein through a cell membrane. At page 4, lines 25-27, it is taught that the secretory processes in yeast were not fully understood. It is also stated at page 16, lines 15-17 that the processing steps for yeast precursor proteins are unpredictably different from those of mammalian precursor proteins.

The specification provides only a single working example of a yeast transformed with an expression vehicle which produces a mature heterologous protein, at pages 25-27, wherein the protein is initially expressed as a fusion with an N-terminus pre-sequence of the first 85 amino acids ending with Arg of yeast alpha mating factor pre-pro protein fused to the mature interferon polypeptide. The specification discloses yeast that can secrete other heterologous proteins that are initially expressed as a

fusion with an 89 amino acid pre-sequence having two Glu-Ala repeats. However, as disclosed on page 20, no "mature" human interferon alpha 1 was produced as the species produced retained both Glu-Ala repeats, and on page 25, only 24% of the bovine interferon produced was processed was "mature", with the major species retaining both Glu-Ala repeats. It is noted that the "mature" protein in these two cases comprised N-terminal amino acids not present in the native mature proteins, being an artifact of the construction of the fusion gene. It is not clear from these results whether fusion proteins lacking these additional amino acids would be properly processed and secreted. Of the remaining examples described by Table I, only trace amounts of rennin and tissue plasminogen activator were secreted and the secreted proteins were not analyzed with respect to complete or proper processing. However based on the results with the two interferon species, one of skill would expect that the other proteins would also be incompletely processed. Furthermore, in the amendment filed 7/22/96 (pages 37-40), Applicant explains the necessity of using only the prepro sequence up to the first Lys-Arg, i.e. the first 85 amino acids. Thus, the production of mature proteins is not enabled.

Szebo et al. (1986) discloses that 95% of a consensus interferon expressed as a pre-pro-alpha-factor fusion protein with or without Glu-Ala repeats at the processing site was retained in the cell (page 5859, col. 2 para. 1; Fig. 3, page 5860). Of the secreted protein, the majority of the protein secreted from the construct having the repeats was properly processed, while 50% of the protein produced from the construct lacking the repeats was unprocessed, i.e. not cleaved at Lys-Arg (page 5860).

Szebo et al. disclose in contrast to their findings, work by others indicated that gene fusions containing the Glu-Ala repeats resulted in the secretion of heterologous proteins with incompletely processed N-termini (page 5860, col. 2). This indicates that one of skill in the art would be unable to accurately predict which proteins might be functional when incompletely processed and retaining some extra amino acids on the end. Clearly, it would also require undue experimentation for said person of ordinary skill to determine how to use a nonfunctional protein.

Finally, (8) the claims are enormously broad because they are not limited to proteins that may be functional when incompletely processed and retain extra amino acids on the end.

The specification teaches generally that at the time the invention was made, the secretory process of yeast was not well understood. The results disclosed in the specification and by Szebo et al., well after the time the invention was made, indicate that secretion of "mature" protein using an alpha factor pre-sequence was unpredictable. Similarly, an extension of the teachings of Szebo et al. and the specification establishes the unpredictability of producing functional protein retaining unprocessed amino acids on the end. Since the specification provides only a single working example of a yeast capable of secreting a mature heterologous protein, the breadth of the claim is not commensurate in scope with the enabling disclosure.

Based on this analysis, the conclusion that it would require undue experimentation to practice the instant invention is inescapable.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

6. Claims 52-54 are rejected under 35 U.S.C. 102(g) as being anticipated by the count of Interference No. 102,728.

The count of Interference No. 102,728 is

A DNA construct comprising a sequence of the following formula:

5'-L-S-Gene*-3', where:

L encodes a Saccharomyces alpha-factor leader sequence recognized by a yeast host for secretion;

S encodes a spacer sequence providing processing signals resulting in the enzymatic processing by said yeast host of a precursor polypeptide encoded by L-S-Gene* into the polypeptide encoded by Gene*, S containing the sequence 5'-R1-R2-3' immediately adjacent to the sequence Gene*, R1 being a codon for lysine or arginine, R2 being codon for arginine, with the proviso that S not contain the sequence 5'-R3-R4-X-3', where R3=R1, R4=R2, and X encodes a processing signal for dipeptidylaminopeptidase A; and

Gene* encodes a polypeptide foreign to Saccharomyces.

The instant claims do not exclude the subject matter of the count and, since the instant applicant lost the interference the count is prior art against the instant applicant.

The DNA construct of the count is a yeast expression vector; thus, claims 52-54 are clearly anticipated.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 47-51 and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over the count of Interference No. 102,728.

The count of Interference No. 102,728 is reproduced above, as the rationale for concluding that it is prior art to the instant applicant.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a DNA construct in accordance with the count with a specific gene and then place it into a yeast cell in order to make and/or secrete the protein with the reasonable expectation of success. This expectation is raised by the conventionality of use of such constructs; in fact, no protein would be produced otherwise.

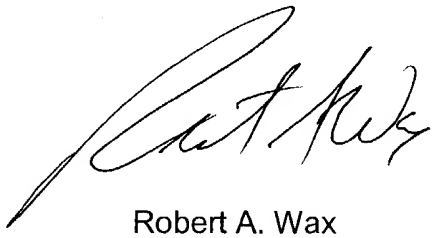
Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert A. Wax
Primary Examiner
Art Unit 1653

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